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Reduction of tertiary lymphoid organs in salivary glands of NOD mice by PI3K-delta inhibition

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Non-obese diabetic (NOD) mice provide a preclinical model of autoimmune diseases as they spontaneously develop autoimmune diabetes sharing many similarities to type 1 diabetes (T1D) as well as sialadenitis, resembling Sjögren's syndrome in humans. In the current study, we followed the natural course of the disease and evaluated the therapeutic effects of a potent and selective PI3Kδ inhibitor referred as "compound-1" (manuscript in preparation). Drug-treatment was administered over 12 weeks, mixed with food at 0.1%, to 12-weeks old NOD mice (n=12). This treatment demonstrated in preliminary studies full target inhibition. In parallel, control NOD mice were given drug-free food (n=12). Blood samples were collected for drug level measurements (LC-MS-MS). Anti-IgM/rIL-4-induced PI3Kδ-dependent pAkt in B cells was used as PD marker and monitored by flow cytometry. The incidence of diabetes, the cellularity of spleen and salivary glands were determined. The number of antibody-secreting cells was measured by ELISPOT. The development of ectopic germinal centers in salivary glands was followed by immunohistochemistry. After 12 weeks of treatment, a similar diabetes incidence was observed in compound-1-treated vs. control NOD mice. Drug blood levels (0.11-1.12 μM) showed an exposure-related inhibition of PI3K/pAkt pathway activation, with a mean IC50 value of approximately 0.44 μM. In the spleens, flow cytometry analysis revealed marked drug-induced reductions in marginal zone B cells (≥70%), in germinal center B cells (≥30%), plasma cells (≥60%) and Tfh cells (≥40%). In salivary glands, significant reductions in infiltrating $CD3^+$ T cells and $CD45R^+$ B cells (≥40%) were observed in drug-treated vs. control NOD mice (Figure 1). In line with this observation, the incidences of IgM-secreting and IgG-secreting cells in salivary glands were significantly reduced (by 70-80%) in drug-treated vs. control mice. In conclusion, this study provides pre-clinical proof-of-concept that PI3Kδ inhibition reduces hallmarks of disease pathology that are operational in Sjögren's syndrome.

Biography

Marc Bigaud holds a PhD degree and is a Senior Pharmacologist at the Novartis Institute for Biomedical Research, in Basel (Switzerland). He is a part of the Auto-Immunity, Transplantation and Inflammation-Disease Area

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